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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

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DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,454	ROIZ ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19 and 21-62* is/are pending in the application.

4a) Of the above claim(s) *8-14,21-44 and 53-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15,16,19,45-52,61 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and Dr. Oded Shoseyov's declaration filed 4-22-04 has been entered. Claims 1, 3-5, 7, 15 and 45-52 have been amended. Claims 17, 18 and 20 have been canceled. Claims 61 and 62 have been added. Claims 1-16, 19 and 21-62 are pending. Claims 1-7, 15, 16, 19, 45-52, 61 and 62 are under consideration.

Priority

1. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must **include the relationship** (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the **first sentence of the specification** following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The amendment filed 4-22-04 on page 1 line 4 of the specification regarding the priority of the present application fails to point out the relationship between PCT/IL00/00514 and Application No. 09/385,411. Appropriate correction is required.

Specification

The amendment filed 4-22-04 amending the specification by inserting on page 1 line 4 "This application is a National Phase application of PCT/IL00/00514... **the contents of which are hereby incorporated by reference**" is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The oath/ declaration only claims priorities of PCT/IL00/00514 and 09/385,411 but fails to incorporate herein by reference. Thus, the amendment filed 4-22-04 introduce new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3, 15, 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 4-22-04 necessitates this new ground of rejection.

The term "and/or" in claims 3 and 15 is vague and renders the claims indefinite. It is unclear what is intended to claim. Changing the term "and/or" to "or...or both" would be remedial. Claims 16 and 19 depend on claim 15 but fail to clarify the indefiniteness.

The term "substantially purified" in claim 15 lines 2 and the term "substantially deglycosylated" in claim 15 line 3 are vague and render the claim indefinite. It is unclear as to

the metes and bounds of what would be considered "substantially purified" and "substantially deglycosylated". Claims 16 and 19 depend on claim 15 but fail to clarify the indefiniteness.

The term "derived from" in claim 15 is vague and renders the claim indefinite. The term "derived from" could mean chemically modified, physically modified, or genetically modified etc. The metes and bounds of the term "derived from" is unclear and the specification fails to define the term "derived from". Claims 16 and 19 depend on claim 15 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7, 15, 16, 19 and 45-52 remain rejected and claims 61 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventively reducing the number of aberrant crypt foci (ACF) in a rat when RNase B1 is administered directly to the colon via osmotic micro-pump, or reducing the number of colon tumor, the tumor size, the number of ACFs or the tumor angiogenesis in a rat with oral administration of the RNase B1 microcapsules, and reducing the number and size of tumor, inhibiting the growth of tumor and reducing angiogenesis of tumor in rats treated with osmotic pumps that directly deliver the RNase B1 to the colon, does not reasonably provide enablement for a method of preventing, treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells,

such as tumor cells, in a subject by using any ribonuclease of the T2 family or its mutants that substantially lack ribonuclease activity via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 11-5-03. Applicant's arguments filed 4-22-04 have been fully considered but they are not persuasive.

The newly added claims 61 and 62 depend on claim 1 and specify the differentiation is malignant differentiation and the angiogenesis is tumor angiogenesis, respectively.

Applicants argue that there is great structural similarities shared by T2 family ribonuclease and one of ordinary skill would understand that all such ribonucleases would have same or similar functional capacities as RNase B1with respect to regulation of mammalian cellular processes. Applicants argue that T2 family ribonucleases share critical structural/functional features such as five conserved disulfide bridges and two conserved active site segments (CAS), and a composition of about 200 amino acid residues, and it would be routine experimentation to use mutants of T2 family ribonucleases for the claimed invention (amendment, p. 16-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03. RNases from T2 family are widespread in distribution and encompass ribonucleases isolated from viruses, bacteria, protozoa, fungi, plants, and animals. Although they share some similar structural features it does not necessarily mean that they would have same biological functions with respect to preventing, treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells in vivo. There are about 50 known T2 family

of ribonucleases having molecular weights ranging from 19kDa to 97kDa and they have diverse role in living organisms. They have dramatically different amino acid sequences. Very few information is available on the structure-function correlation except that of RNase Rh and RNase LE. As discussed in the preceding Official action mailed 11-5-03, the biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. One skilled in the art at the time of the invention would not know how to use the full scope of the T2 family ribonucleases and their mutants for preventing, treating, inhibiting, or reversing proliferation, development, tumor growth, tumorigenesis, colonization, differentiation or angiogenesis of abnormally proliferating cells in vivo.

Applicants argue that claims 4 and 5 each depend from claim 1 and examiner inappropriately linked claim 5, drawn to different administration modes, with claim 4, drawn to different types of diseases, and the instant invention is drawn to the use of T2 family RNase as therapeutic agent effective against abnormally proliferating cells, such as tumor cells, in a mammalian subject. Applicants further argue that the effect of T2 RNases is not administration mode-dependent but rather concentration-dependent (amendment, p. 18). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03. Claim 1 encompasses any abnormally proliferating cells which include the abnormally proliferating cells associated with the diseases or disorders recited in claim 4, and any administration routes including those recited in claim 5. Therefore, claims 1 and 4 encompass preventing, treating, inhibiting, or reversing the abnormally proliferating cells recited in claim 4 via various administration routes including those recited in claim 5. Claims 1 and 5 encompass preventing, treating, inhibiting, or reversing the abnormally proliferating cells including those

recited in claim 4 via various administration routes as recited in claim 5. As discussed in the preceding Official action mailed 11-5-03, the amount of protein that reach the target cells, the stability of the protein, the protein's compartmentalization within the cell, the type of target cells, the biological function of the protein, and the immune response of the host cells against the protein are all important factors that affect the efficiency of the protein therapy of various diseases in vivo. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids, and there is blood-brain barrier for treating brain tumors. The claims encompass numerous different diseases or disorders including papilloma, kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, thyroid cancer, leukemia, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc. The claims encompass treating abnormally proliferating cells residing at various locations all over the body of a mammalian subject. Thus, the effectiveness of the T2 family RNases or their mutants on preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders would depend on administration route of the claimed RNases and may also depend on their concentrations. Administration routes of the claimed RNases will determine whether sufficient RNases can reach target cells so as to provide therapeutic effect for preventing, inhibiting, or reversing various abnormally proliferative cells associated with different disorders or diseases in vivo. Further, each member of T2 family RNases has different biological function and the effective amount of RNase at the target cells could vary, therefore,

one skilled in the art at the time of the invention would require undue experimentation to determine the amount of the RNase administered and the administration route for said RNase so as to provide therapeutic effect for various diseases and disorders in vivo for the full scope of the invention claimed.

Applicants argue that administration of T2 family RNases via microcapsules can be easily optimized for therapeutic effectiveness and it is routine experimentation (amendment, p. 19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03 and the reasons set forth above.

Applicants argue that the specification teaches administering RNase for treating a digestive tract disease, such as colon cancer, via intra-digestive tract osmotic pump and it is routine experimentation to deliver T2 family RNase to essentially any desired target tissue via a suitable route (amendment, p. 19). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03 and the reasons set forth above. Administering RNase to a digestive tract disease, such as colon cancer, via intra-digestive osmotic pump is similar to directly administer RNase to target site, which is only one type of administration route. The claimed invention encompasses various administration routes for preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders in vivo.

Applicants cite patents 6,416,960 ('960), 6,075,009 ('009), and 6,306,832 ('832) and argue that those patents teach administering polypeptide to a subject via various administration routes and the specification provides sufficient guidance to enable the claimed invention (amendment, p. 20). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03 and the reasons set forth above. Patents '960 and '009

only teach administering polypeptide to a subject but not for preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders in vivo. Patent '832 teaches administering a polypeptide having the sequence of SEQ ID No. 39 to a subject for treating breast cancer. The polypeptide having amino acid sequence of SEQ ID No. 39 is totally different from the T2 family RNases and they have totally different biological functions. Each protein therapy has to be considered individually because of the different biological function of the protein used and various factors including administration routes as mentioned before that determine whether sufficient protein is obtained at target cells so as to provide therapeutic effect in vivo. Further, patent '832 only limits to treating breast cancer, however, the present invention encompasses preventing, inhibiting, or reversing any abnormally proliferating cell associated with numerous different diseases or disorders including papilloma, kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, thyroid cancer, leukemia, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc., in vivo. Thus, one skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed.

Applicants cite Dr. Shoseyov's declaration and argue (i) the RNase is any of various RNases of the T2 family; (ii) the administration of the RNase is effected via various routes; (iii) the abnormally proliferating cells include different types of cancer cells; and (iv) the process associated with abnormally proliferating cells includes various pathologic processes (amendment, p. 20-21). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 11-5-03 and the reasons set forth above. The data regarding T2

family RNase other than RNase B1, such as Aspergillus oryzae RNase T2, E. coli RNase I, and RNase 6PL, are all in vitro data, which can not be extrapolated into success in in vivo. The in vivo data provided in the specification and the declaration are only for RNase B1. As discussed above, there are about 50 known T2 family of ribonucleases having molecular weights ranging from 19kDa to 97kDa and they have diverse role in living organisms. They have dramatically different amino acid sequences and the effective amount of the RNase required to provide therapeutic effect in vivo could vary. Very few information is available on the structure-function correlation except that of RNase Rh and RNase LE. Each protein therapy has to be considered individually because of the different biological function of the protein used and various factors including administration routes as mentioned before that determine whether sufficient protein is obtained at target cells so as to provide therapeutic effect in vivo. Further, the claims encompass numerous different diseases or disorders including papilloma, kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, thyroid cancer, leukemia, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc. The claims encompass treating abnormally proliferating cells residing at various locations all over the body of a mammalian subject. Thus, the effectiveness of the T2 family RNases or their mutants on preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders would depend on the RNase used and the administration route of said RNase.

Regarding the in vivo data provided by Dr. Shoseyov's declaration, the melanoma cells were injected i.p. into mice and the RNase B1 was also injected i.p. into mice, and the cells were

injected via lateral tail vein and the RNase B1 was injected by the same manner (declaration, p. 3). Such administration of the RNase is similar to direct injection to the target cells. When the tumor cells and the RNase are injected into mice by the same route, one would expect the RNase would reach the same site as the injected tumor cells. This is dramatically different from administering RNase to a mammalian subject having naturally occurring and pre-existing solid tumors or other type of tumors. When cancer cells were injected subcutaneously or systemically (intravenous or i.p.) and the i.p. injected RNase B1 inhibits tumor cell growth subcutaneously or inhibits lung metastasis (declaration, p. 5-6, 8-9), such data only provides evidence of the effect of RNase B1 for the particular administration route for the particular location of target cells but not the full scope of the invention claimed. The claims encompass numerous different diseases or disorders including papilloma, kaposi's sarcoma, melanoma, lung cancer, ovarian cancer, prostate cancer, astrocytoma, head cancer, neck cancer, bladder cancer, breast cancer, thyroid cancer, leukemia, Hodgkin's disease, Burkitt's disease, arthritis, rheumatoid arthritis, diabetic retinopathy, restinosis, vascular graft restenosis etc. The claims encompass treating abnormally proliferating cells residing at various locations all over the body of a mammalian subject. As discussed above, the effectiveness of the T2 family RNases or their mutants on preventing, inhibiting, or reversing the abnormally proliferating cells associated with various diseases or disorders would depend on the RNase used and the administration route of said RNase in vivo. One skilled in the art at the time of the invention would require undue experimentation to practice over the full scope of the invention claimed. Thus, claims 1-7, 15, 16, 19 and 45-52 remain rejected and claims 61 and 62 are rejected under 35 U.S.C. 112 first paragraph.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Nomachi et al., 1980 (J. Gen. Appl. Microbiol., Vol. 26, p. 375-385). Applicants' amendment filed 4-22-04 necessitates this new ground of rejection.

Claims 15 and 16 are directed to a pharmaceutical composition comprising a substantially purified ribonuclease of the T2 family derived from Aspergillus niger, and a pharmaceutically acceptable carrier. Claim 16 specifies the ribonuclease of T2 family substantially lacks ribonucleolytic activity.

Nomachi teaches purification of RNases I and II from Aspergillus niger by using DEAE-cellulose column chromatography and the RNases were eluted with 0.01M Tris-HCl buffer (e.g. p. 377). The optimal pH of acid RNase I was pH 3.5, whereas that of II was pH 4.5 (e.g. p. 378). Acid RNase I lost its whole activity over 70°C at pH 4.5 (e.g. p. 379). The Tris-HThus, claims 15 and 16 are anticipated by Nomachi.

It should be noted that the term "pharmaceutical" does not carry weight when a 102 or 103(a) rejection are being considered.

8. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Horitsu et al., 1974 (Agr. Biol. Chem., Vol. 38, No. 5, p. 933-940). Applicants' amendment filed 4-22-04 necessitates this new ground of rejection.

Claims 15 and 16 are directed to a pharmaceutical composition comprising a substantially purified ribonuclease of the T2 family derived from Aspergillus niger, and a pharmaceutically acceptable carrier. Claim 16 specifies the ribonuclease of T2 family substantially lacks ribonucleolytic activity.

Horitsu teaches purification of RNase from Aspergillus niger NRC-A-1-233 by using DEAE-cellulose column chromatography and the RNase was eluted with 0.025 M phosphate buffer containing 0.4 M NaCl, and after Sephadex G-75 gel filtration, the collected fractions were dialyzed against distilled water (e.g. p. 935, right column to p. 936, left column). The optimal pH of the RNase activity was pH 3.5 (e.g. p. 937, right column to p. 938, left column). The SDS-PAGE gel will denature the RNase protein and substantially inactivate its ribonucleolytic activity (e.g. p. 937, right column). The 0.025 M phosphate buffer containing 0.4 M NaCl or the distilled water Thus, claims 15 and 16 are anticipated by Horitsu.

It should be noted that the term "pharmaceutical" does not carry weight when a 102 or 103(a) rejection are being considered.

Conclusion

No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.